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REVIEW

Ce6 nanoassemblies: Molecular mechanism and strategies for combinational anticancer therapy

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Abstract

Nowadays, cancer has become the leading cause of death worldwide, driving the need for effective therapeutics to improve patient prognosis. Photodynamic therapy (PDT) has been widely applied as an antitumor modality, owing to its minimal invasiveness, localized tumor damage, and high safety profile. However, its efficacy is limited by poor stability of photosensitizers, inadequate tumor accumulation, and a complex tumor microenvironment. To overcome these challenges, extensive endeavors have been made to explore the co-assembly of the widely used photosensitizer chlorin e6 (Ce6) with various functional small molecules to enhance pharmacodynamic activity. This review provides a comprehensive overview of current studies on Ce6-based nanoparticles for effective PDT and precise delivery of functional molecules. The self-assembly mechanism will be discussed in detail, with a focus on potential strategies for combinational therapy with PDT.

KEYWORDS

cancer treatment, carrier-free, chlorin e6 (Ce6), light, nanomedicine, photodynamic therapy (PDT), self-assembly

1 | INTRODUCTION

Precise targeting of drug molecules is the key to medicine development for malignancies. Nanomedicine has been extensively investigated to achieve tumor-targeted drug delivery, due to its excellent in vivo behaviors such as prolonged blood circulation and tumor-specific accumulation.[1] As demonstrated by the well-known enhanced permeation and retention (EPR) effect, nano-sized vesicles tend to accumulate in tumor tissues.[2] Nowadays, tremendous effort has been made to develop delicately designed nanocarriers such as liposomes,[3] polymeric nanoparticles,[4] and membrane-coated vesicles.[5] However, the clinical translation of those formulations is hindered by the complicated fabrication processes, low drug-loading capacity and potential immunogenicity of excipients.[6,7] Carrier-free nanoparticles based on self-assembly have attracted soaring interest in recent years due to their simple preparation, high drug-loading efficiency, and minimized immunogenicity.[8,9] Moreover, the high thermodynamic stability and potential scalability further increase the possibility of its clinical translation.[10]

Photodynamic therapy (PDT) has been considered as one promising tool for anticancer treatment. By combining non-invasive light irradiation and photosensitizers, reactive oxygen species (ROS) can be generated to induce cell autophagy, apoptosis and necrosis.[11,12] Chlorin e6 (Ce6) is aU.S. Food and Drug Administration (FDA)-approved photosensitizer with a high quantum yield of singlet oxygen and good biocompatibility.[13,14] However, Ce6 is highly hydrophobic and easily aggregates in physiological environment, which limits its tumor accumulation.[15] Besides, sole PDT hardly eradicates tumors due to the complicated tumor microenvironment that support tumor survival and escape from PDT. Therefore, it is desired to develop efficient drug delivery systems to improve the PDT efficacy of Ce6.

Recent research has demonstrated that Ce6 can serve as both a potent ROS producer and a stabilizer in drug delivery systems. By virtue of its planar conjugated structure and hydrophobicity, it is likely for Ce6 to interact with other functional molecules through π-π stacking and hydrophobic interactions.[16] Moreover, compared with other photosensitizers, the carboxyl groups of Ce6 that can undergo protonation/deprotonation processes enable potential interaction with other therapeutic molecules by electrostatic interaction and hydrogen bonding.[17] Therefore, Ce6 represents a good candidate for molecular self-assembly. Carrier-free co-delivery

of Ce6 and other small-molecule drugs can not only improve their pharmacokinetic profiles but also enhance PDT efficacy with aligned synergistic pharmacological functions.[1] The good biocompatibility and high quantum yield of ROS upon light irradiation of Ce6 guaranteed its safety in dark conditions and efficient treatment efficacy at the desired area under specific light irradiation.[13] The Ce6-based nanoparticles with optimized size can take advantage of the EPR effect for enhanced tumor accumulation. Potential immunogenicity and toxicity from additional excipients can be minimized owing to the inherent carrier-free characteristics. Furthermore, the straightforward preparation process enables scalable production, provided that minimized batch-to-batch variation can be accomplished.

In this review, we provide a brief introduction of clinical application of PDT and a summary of the latest studies on co-assembly of Ce6 and therapeutics such as synthetic molecules and peptides. The rational design, self-assembly mechanisms, and preparation method of Ce6-incorporated nanoparticles are discussed. Moreover, potential combinational use of Ce6-based PDT is emphasized to provide a detailed reference for future molecular design of Ce6-based nano drug delivery systems.

2 | CLINICAL TRIALS OF PDT

PDT, as an alternative to chemotherapy and radiation therapy, has been applied in clinical use since 1980s by virtue of its minimal invasiveness, localized tumor damage, and high safety.[18] There are two steps involved to achieve effective PDT including injecting photosensitizers intravenously or directly to tumor sites and then applying light irradiation at the tumor lesions. PDT efficacy has been proven in several cancer types such as melanoma,[19] esophageal cancer,[20] lung cancer,[21] etc.

Chlorins are a class of porphyrin-based photosensitizers containing chromophore molecules.[22] When exposed to light irradiation, chromophore molecules can transfer energy to oxygen to generate ROS, which exerts substantial damage to tumor cells and stimulate the anticancer activity of the immune system.[23] Some chlorin-family photosensitizers have already been approved by the FDA, such as Foscan, Photofrin, and Visudyne, and the excitation wavelength of these photosensitizers has been extended from 630 to 749 nm.[24] Ce6 is a second-generation, FDA-approved photosensitizer (FDA UNII: 5S2CCF3T1Z) with improved pharmacokinetic properties. There are several completed clinical trials of Ce6 and its derivatives. For example, the treatment efficacy of mono-L-aspartyl Ce6 was confirmed in superficial squamous cell carcinoma of the lung.[25,26] As a result, it was approved for the treatment of lung cancer in Japan.[27] Moreover, a phase 2 clinical trial of a Ce6 derivative was completed to investigate its efficacy to treat denture stomatitis as an antimicrobial agent (NCT04532060).

However, the efficacy of PDT is often undermined by poor cellular uptake and unsatisfactory biodistribution of photosensitizers, which leads to mild but long-lasting phototoxicity like burning and swelling pain in normal tissues.[28] Moreover, deficient tissue penetration of light limits the usage of PDT for skin cancer or small superficial tumors below the skin surface. In recent years, nanoscale drug delivery systems have shown great benefits in improving drug delivery efficacy with reduced side effects. For this reason, constructing nanosystems based on photosensitizers has become an attractive strategy to overcome the above-mentioned limitation of PDT. Specifically, Ce6 can self-assemble with other molecules to form nanoparticles owing to its special chemical structures and hydrophobicity. The carrier-free drug delivery system not only avoids the potential immunogenicity from excipients but also retains the "nanoscale advantages" such as improved tumor penetration, tumor accumulation, and blood circulation. The desire to exploit these advantages has motivated recent tremendous efforts to develop Ce6-based nano drug delivery systems and facilitated its potential future clinical translation.

3 | PREPARATION METHOD AND SELF-ASSEMBLY MECHANISM FOR CE6-BASED NANOPARTICLES

The principle of Ce6-incorporated nanoparticles is based on self-assembly of Ce6 and other molecules. Currently, the most widely used preparation method is via nanoprecipitation.[29] With the method, drug molecules are dissolved in an organic solvent (such as DMSO or ethanol) and then added dropwise into water. Subsequently, the nanoparticles will be formed under continuous stirring or vortex. To purify nanoparticles, there are two ways, namely dialysis and centrifugation. For dialysis, the obtained nanoparticle solution can be dialysed against phosphate buffered saline(PBS) to remove free drug molecules.[30] For the other modality, low-speed centrifugation will be utilized to remove big precipitates, while high-speed centrifugation will be exploited to collect nanoparticles with narrow size distribution.[31,32]

The driving forces promoting the self-assembly of Ce6 and hydrophobic molecules were investigated in several studies.[33,34] As shown in Figure 1A, the conjugated structure based on double bonds and planar structure of Ce6 provide potential interactions with other molecules through hydrophobic interaction and π-π stacking. Moreover, the carboxyl groups provide potential electrostatic interaction and hydrogen bonding with other molecules.

For example, a drug delivery system self-assembled from Ce6 and hydrophobic drug MK-0752, a Notch pathway inhibitor, was constructed.[32] Molecular docking analysis predicted the major interaction forces driven for the self-assembly of the two molecules were hydrophobic interaction, π-π stacking and electrostatic interaction. Subsequently, ultraviolet-visible (UV-Vis) spectrum was monitored to further study the interaction forces. As shown in Figure 1C, the monomeric Ce6 exhibited characteristic peak around 660 nm in methanol while they transferred into aggregated state due to unsatisfactory solubility in water, showing featured peak around 640 nm. In particular, the co-assembly of Ce6 with MK-0752 in water resulted in the presence of the peaks at both 640 and 660 nm, implying defective aggregation of Ce6 after the self-assembly. The phenomenon confirmed the molecular interaction between Ce6 and MK-0752. To further investigate the driving forces behind, sodium dodecyl sulfate (SDS) was added into the solution of nanoparticles, which caused an increase in the absorption peak of UV-Vis

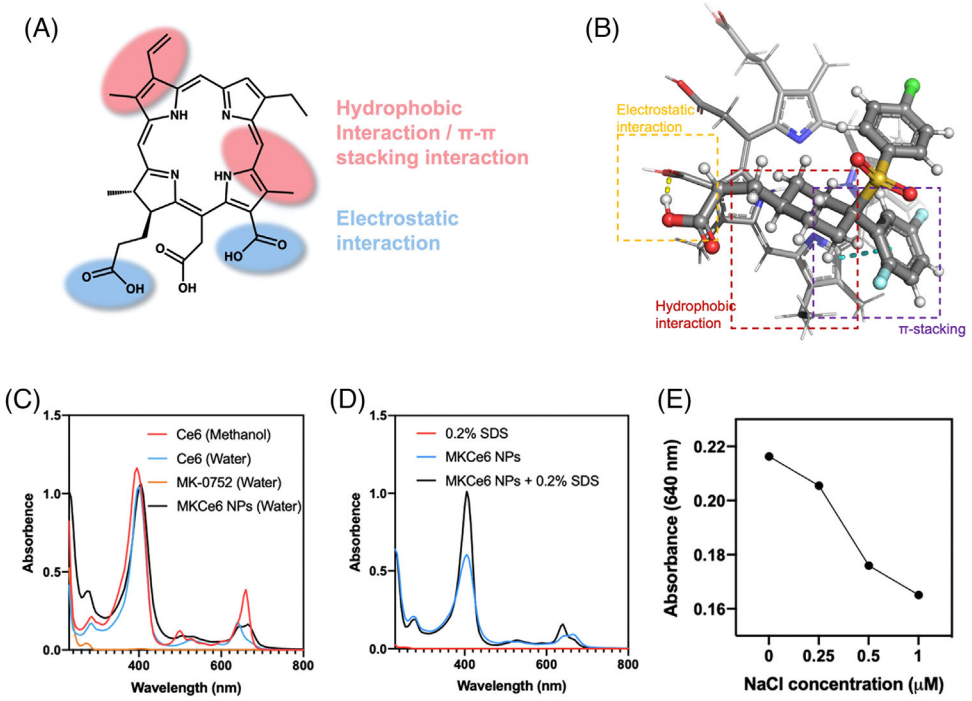


FIGURE 1 The proposed mechanism for Ce6-driven self-assembly. (A) A schematic illustration of chemical structure of Ce6 for self-assembly with other molecules. (B) Molecular docking analysis of self-assembly between Ce6 and MK-0752. (C) UV-Vis absorption spectra of monomeric Ce6, aggregated Ce6, and self-assembled nanoparticles. (D) UV-Vis absorption spectra of self-assembled nanoparticles with or without SDS. (E) UV-Vis absorption of self-assembled nanoparticles at 640 nm in solutions with varying salt concentrations. Figure 1B–E were derived from Ref.[32] with permission from © 2022 the authors. Aggregate published by SCUT, AIEI, and John Wiley & Sons Australia, Ltd.

spectrum (Figure 1D). The result indicates hydrophobic interactions are highly involved in the self-assembly process of Ce6 with hydrophobic molecules. Furthermore, the turbidity of Ce6-based self-assembled nanoparticles decreases with addition of sodium chloride (NaCl), indicating the destruction of electrostatic forces in nanoassemblies (Figure 1E).

Apart from hydrophobic molecules, recent research indicates that it is feasible for Ce6 to self-assemble with hydrophilic molecules by virtue of its three ionizable carboxylic acids.[35] The strong interactions of hydrogen bonds and electrostatic interaction can facilitate stable co-assembly of Ce6 and hydrophilic molecules under certain circumstances.

To be concluded, the pyrrole groups of Ce6 can interact with conjugated structure of other molecules via hydrophobic interaction and π-π stacking. The carboxyl groups of Ce6 can interact with other molecules by electrostatic interaction and hydrogen bonding. The controllable self-assembly process of Ce6 with other molecules is of great interest to form drug delivery systems with diverse functions. By discovering more molecules with right chemical structure such as conjugated chain, hydrophobic structure, deprotonated groups and so on, more versatile and flexible smart drug delivery systems can be built.

4 | CE6-BASED SELF-ASSEMBLED NANOPARTICLES FOR COMBINATIONAL THERAPY WITH PDT

Despite the strong cytotoxicity of PDT, the anticancer effect may be attenuated due to the heterogeneity of tumor cells, which may result in poor response to PDT. Apart from tumor cells, another factor that undermines PDT efficacy is the tumor microenvironment (TME), which plays a critical role in facilitating tumor progression, metastasis, and recurrence.[36,37] TME is composed of an orchestrated network of vasculature, stromal cells, extra-cellular matrix (ECM), immune cells, different cellular secretory factors, and other components, which collectively provide a favorable place for the growth of tumor cells.[38,39] To enhance the PDT efficacy in cancer patients, a large number of combined treatment methods have been developed. These combination therapies can be categorized into two strategies based on their mechanisms, including directly interacting with tumor cells and remodeling tumor microenvironment (Figure 2).

The first strategy that directly interacts with tumor cells aims to address the problem of PDT resistance. The combinational therapy includes concurrently killing tumor cells or elevating the sensitivity of tumor cells to PDT. Chemotherapy[40] and photothermal therapy (PTT)[41] have been widely investigated as candidates for combination therapy with PDT. Chemotherapy and PTT can directly kill proliferating tumor cells and induce cell apoptosis, eradicating tumor cells with PDT resistance and combating solid tumors synergistically. Another modality, which aims to enhance the PDT sensitivity of tumor cells, can be achieved by acting on the regulating pathway of tumor cells like inhibiting tumor cell respiration to increase oxygen content within tumor cells,[30] deactivating cancer stemness-related pathways to restrain tumorigenicity,[42] etc.

The second strategy for combinational therapy to enhance PDT efficacy is remodeling tumor microenvironment to destroy the "soil" for tumor growth. In particular, accumulated evidence indicated that PDT could not only trigger cell apoptosis but also evoke antitumor immune responses

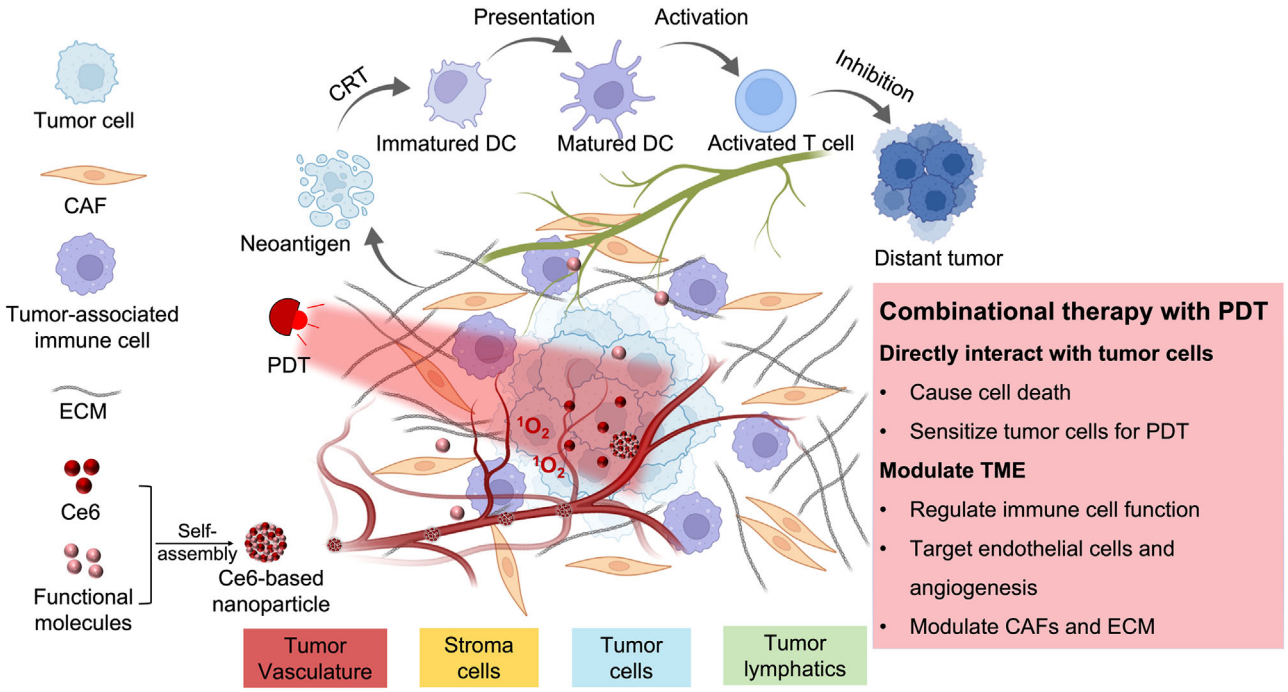


FIGURE 2 Ce6 can self-assemble with functional molecules into nanoparticles to achieve combinational therapy. The functional molecules work in two distinct manners to improve cancer therapy: directly interacting with tumor cells and modulating tumor microenvironment (TME). The solid tumor consists of four parts: tumor vasculature, stroma cells, tumor cells, and tumor lymphatics. Functional molecules can act on these four parts to improve the therapeutic effects of PDT. CAFs (cancer-associated fibroblasts), ECM (extra cellular matrix), CRT (calreticulin), PDT (photodynamic therapy).

by inducing an immunogenic cell death (ICD) cascade.[43] The ROS generation by PDT would destroy tumor cells while producing neoantigen to promote the maturation and migration of dendritic cells (DCs) to recruit and activate cytotoxic T lymphocytes (CTLs). Therefore, the combination of PDT with immune therapy is expected to achieve synergistic anticancer effects. Beyond repressed immune microenvironment, tumor cells rely on abundant and developed vasculature to transport enough oxygen and nutrition to satisfy their vicious proliferation.[44] Consequently, antiangiogenesis arises as a conspicuous strategy to be combined with PDT. Moreover, other important cells like CAFs and ECM,[45] which play important roles in secreting cytokines, promoting metastasis, connecting, etc., can also become a target for combinational therapy.

Currently, there have been many research reports based on Ce6 self-assembly. According to the functions of the co-assembled compounds as mentioned above, we classify them into two types: directly interacting with tumor cells and modulating tumor microenvironment. They tend to co-assemble with Ce6 into nanoparticles driven by hydrophobic interaction, π-π stacking interaction, electrostatic interaction and hydrogen bonding. The chemical structure and functionalities of co-assembled molecules were summarized in Table 1.

4.1 | Directly interacting with tumor cells

As mentioned before, in order to address the problem of PDT resistance resulting from tumor heterogeneity, one modality is exploiting methods directly interacting with tumor cells with other functions. Based on current research, the strategy can be divided into two directions: to directly kill cancer cells through chemotherapy, phototherapy, etc. to achieve combined therapeutic efficacy with PDT; and to elevate the sensitivity of tumor cells towards PDT by deactivating certain pathways.

4.1.1 | Chemotherapy

Chemotherapeutics can be plant-derived or of synthetic origin. They exhibit high cytotoxicity and remain the most common method for cancer treatment.[46] However, the multidrug resistance (MDR) greatly compromised the chemotherapeutic efficacy due to drug efflux from tumor cells.[47] Thus, a combinational approach with PDT that can overcome the chemo drug resistance to concurrently eradicate tumor bulks is highly desired.

To our best knowledge, the first combinational strategy for tumor theranostics was proposed via simple self-assembly of the most commonly used chemodrug doxorubicin (DOX) and Ce6 (Figure 3A).[48] The self-assembled nanoparticles (NPs) exhibited effective tumor eradication without recurrence during one treatment cycle. Meanwhile, no activation of inflammatory and immune responses was observed by virtue of free carriers. The research based on similar mechanism was continued. For example, it is found that Ce6 could self-assemble with a broad-spectrum antitumor drug paclitaxel (PTX) that was extensively used in clinics and a hydrophilic cyanine dye IR783.[49] In the design, Ce6 was utilized as a sonosensitizer and the nanodrug exhibited ultrasonic-responsive drug release with photoacoustic imaging capability by IR783.

Nanodrugs co-assembled by Ce6 with natural alkaloid camptothecin (CPT) and its derivatives, which functioned as topoisomerase I inhibitors, were also farbicated.[50,51] For example, 7-ethyl-10-hydroxycamptothecin (SN38) can

TABLE 1 A table summarizes existing studies of functional molecules that can co-assemble with Ce6.

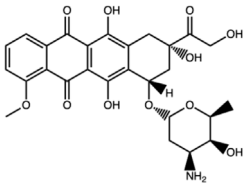
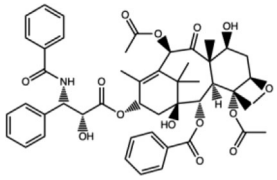
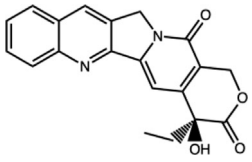
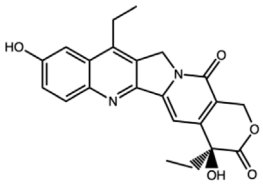
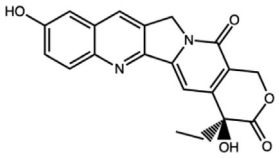
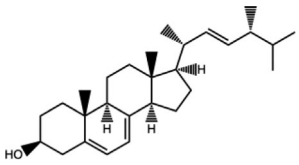
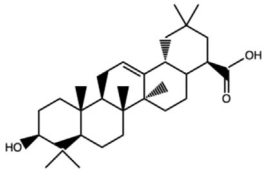
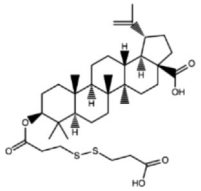
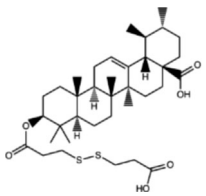
Name	Chemical structure	Function	Ref
Doxorubicin (DOX)		Chemotherapy	[48]
Paclitaxel (PTX)		Chemotherapy	[49]
Camptothecin (CPT)		Chemotherapy	[51]
7-ethyl-10-hydroxycamptothecin (SN38)		Chemotherapy	[51]
10-hydroxycamptothecin (HCPT)		Chemotherapy	[52]
Ergosterol		Chemotherapy	[54]
Oleanolic acid		Chemotherapy	[56]
Betulinic acid modified with disulfide		Chemotherapy, GSH-responsiveness	[57]
Ursolic acid modified with disulfide		Chemotherapy, GSH-responsiveness	[58]

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TABLE 1 (Continued)

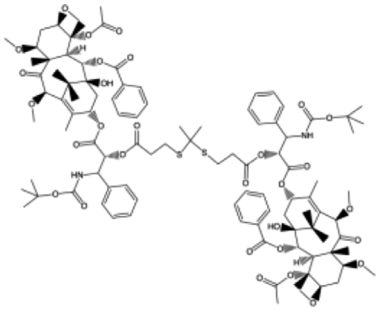
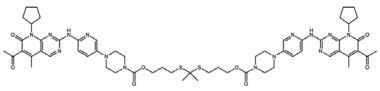
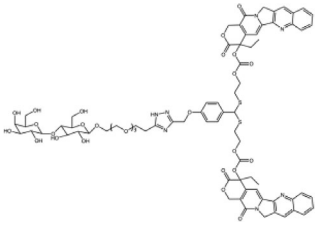
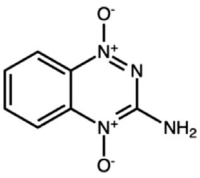
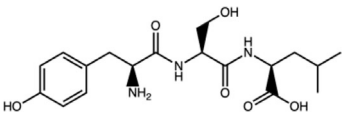
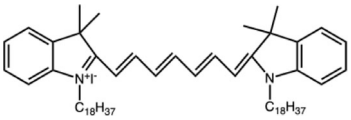
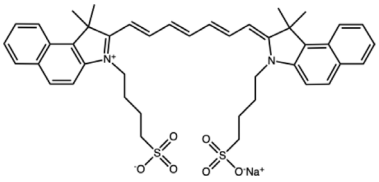
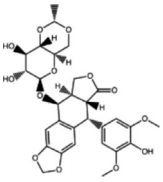
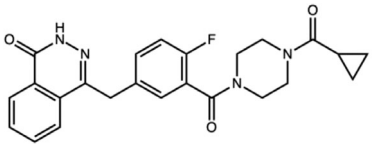
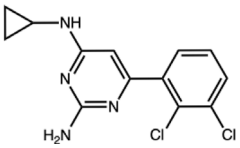
Name	Chemical structure	Function	Ref
Cabazitaxel dimer linked with thioketal linker		Chemotherapy, ROS-responsiveness	[59]
Palbociclib dimer linked with thioketal linker		Chemotherapy, ROS-responsiveness	[62]
Dimeric CPT and lactose linked with aromatized thioacetal		Chemotherapy, ROS-responsiveness	[64]
Tirapazamine		Chemotherapy	[35]
Tyroserleutide (YSL)		Chemotherapy	[68]
1,1′- dioctadecyl-3,3,3′,3′-tetramethylindotricarbocyanine iodide (DiR)		Photothermal therapy	[72]
Indocyanine green (ICG)		Photothermal therapy	[73]
Etoposide (VP-16)		DNA replication and repair inhibitor	[76]
Olaparib		PARP inhibitor, DNA repair damage	[77]
TH588		Mut-T homolog 1 protein inhibitor, facilitating DNA misrepair	[78]

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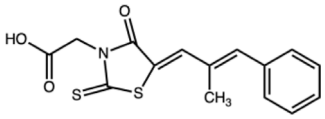
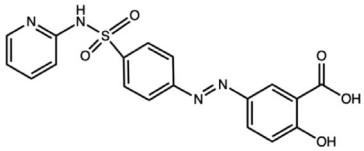
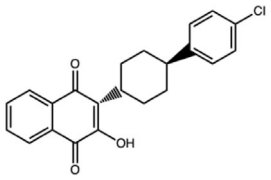
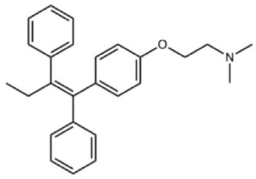
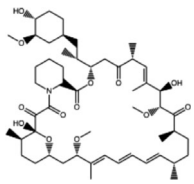
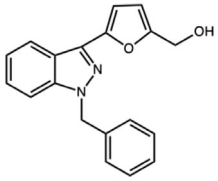
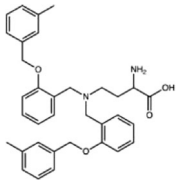
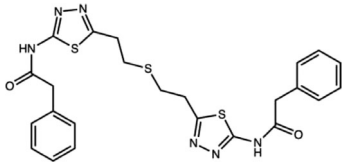
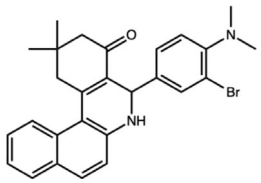
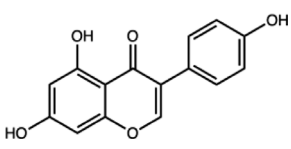
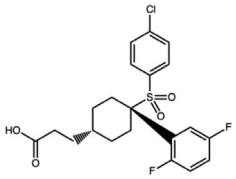
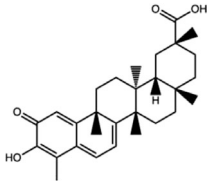
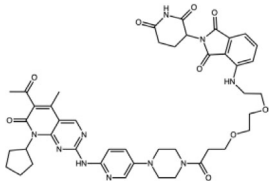
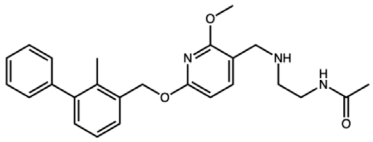
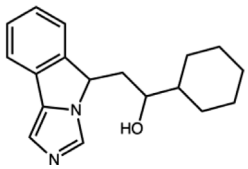
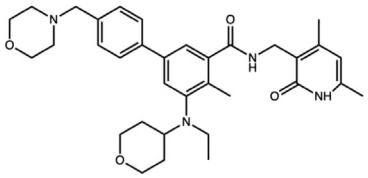
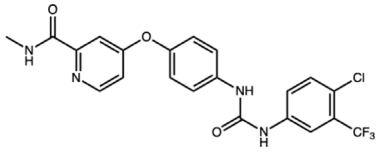
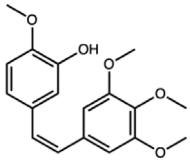
TABLE 1 (Continued)

Name	Chemical structure	Function	Ref
Epalrestat (Epa)		Epithelial–mesenchymal transition (EMT) inhibitor	[81]
Sulfasalazine (SAS)		Anti-inflammatory molecule	[82]
Atovaquone (ATO)		OXPHOS metabolic pathway inhibitor	[30]
Tamoxifen		Inhibiting mitochondrial respiration and reducing Bcl-2 expression	[84]
Rapamycin		Rapamycin inhibitor, inhibiting hypoxia-inducible factor (HIF)-1 function	[87]
3-(5′-hydroxy-methyl-2′-furyl)−1-benzylindazole (YC-1)		HIF-1α inhibitor	[88]
V9302		Glutamine starvation	[91]
Bis-2-(5-phenylacetamido-1,3,4-thiadiazol-2-yl) ethyl sulfide (BPTES)		Glutamine starvation	[92]
Compound 968 (C968)		Glutamine starvation	[93]
Genistein		Glucose starvation	[94]

(Continues)

TABLE 1 (Continued)

Name	Chemical structure	Function	Ref
MK-0752		Gamma-secretase inhibitor, deactivating Notch pathway	[32]
Celastrol		Autophagy promoter	[96]
CDK4/6 PROTAC		Cell cycle arrest	[99]
BMS-202		Immunotherapy, PD-1/PD-L1 blockade	[103]
NLG-919		Immunotherapy, indoleamine 2,3-dioxygenase 1 inhibitor	[33]
Tazemetostat		Immunotherapy, promoting T cell recognition	[106]
Sorafenib		Anti-angiogenesis therapy	[111]
Combretastatin A4 (CA4)		Anti-angiogenesis therapy	[112]

co-assemble with Ce6 into rod-like SN38/Ce6 NPs and spherical-like SN38/Ce6 NPs.[51] The obtained SN38/Ce6 NPs exhibited high drug loading content, excellent stability and high tumor accumulation, which facilitated synergistic chemo-photodynamic therapy under light illumination. Moreover, the driving forces for the self-assembly were explored based on substantial experimental data and visualized docking images. Other derivatives of CPT have also been exploited as prominent and broad-spectrum chemotherapeutic agents for combinational treatment with Ce6. 10-hydroxycamptothecin (HCPT) can co-assemble with Ce6 into uniform nanorods and exhibit substantial antitumor efficacy upon laser irradiation, with no apparent hepatic or renal toxicity shown.[52] The higher cell internalization and enhanced tumor accumulation of the designed system verify that this co-assembly strategy can improve the delivery efficiency of the dual drugs.

Natural products derived from Traditional Chinese Medicine have inherent characteristics of good biodegradability and biocompatibility. An extract from fungi and

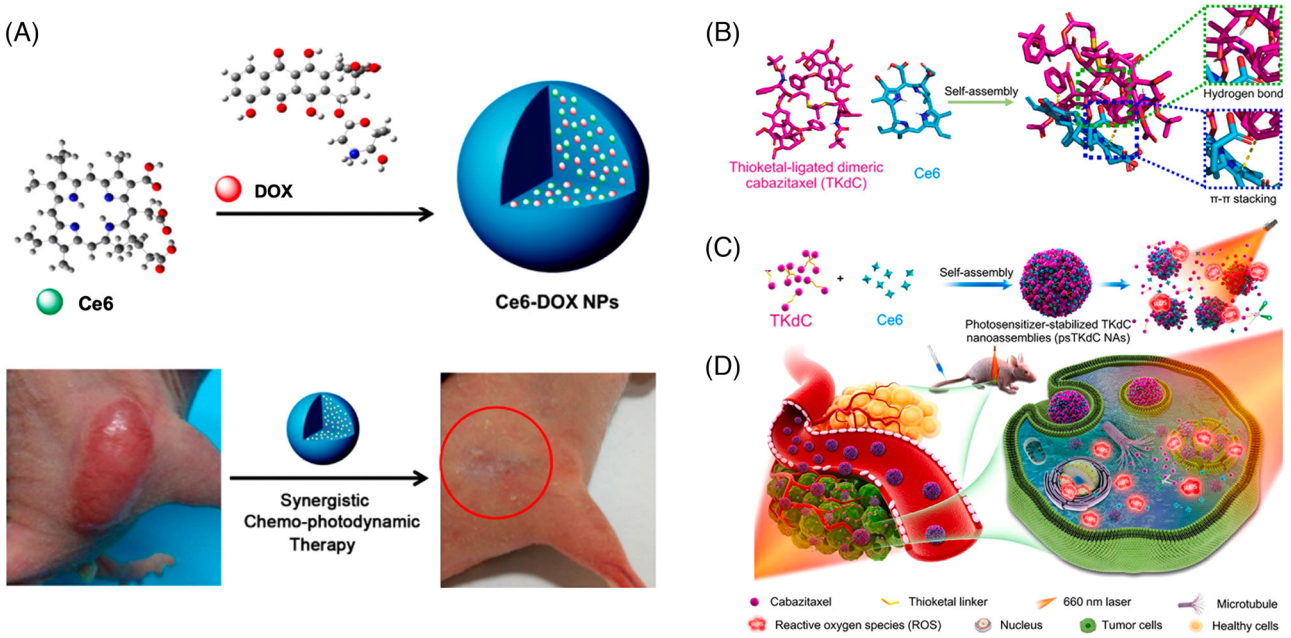


FIGURE 3 Schematic representation of carrier-free nanoparticles via co-assembly between chemotherapeutics and Ce6. (A) The self-assembly of Ce6 and DOX for combination of chemotherapy with PDT. Figure reproduced from Ref.[48] with permission. Copyright © 2016 American Chemical Society. (B) The self-assembly of Ce6 and dimeric CTX for synergistic photo/chemotherapy and molecular docking analysis investigating the intermolecular interactions. (C) The diagram depicting the nanoparticle's self-assembly process and drug release in response to NIR light irradiation. (D) Schematic illustration of the self-assembled nanoparticles for synergistic photo/chemotherapy in vivo. Figure reproduced from Ref.[59] with permission. Copyright © 2020 Elsevier B.V.

protozoa, named ergosterol, can activate the apoptotic signal pathway and serves as a potential lead for cancer therapy.[53] Based on this, a nanoparticle co-assembled from Ce6 with ergosterol was faricated.[54] Subsequent pharmacodynamic study showed remarkable antitumor activity, which provides a perspective to develop more self-assembled nanomaterials with natural small molecules to treat various malignancies. Similarly, they screened out 11 terpenoid compounds that could form co-assembled nanoparticles with Ce6 with regulatable drug sizes.[55] In addition, oleanolic acid, a natural pentacyclic triterpene, was reported to be able to self-assemble with Ce6 into spherical nanoparticles with a uniform size around 100 nm, which achieved a synergistic chemo/sono-photodynamic therapy for cancer treatment.[56]

Moreover, small molecules can be endowed with responsiveness by conjugating with responsive linkers. For example, pentacyclic triterpenes of betulinic acid (BA) modified with glutathione (GSH)-responsive linker can co-assemble with Ce6 for redox-triggered targeted cancer treatment.[57] Owing to the overexpressed GSH in the tumor microenvironment, the prodrug could quickly release activated BA to effectively kill cancer cells. The depletion of GSH would facilitate PDT effect in turn. Moreover, the molecular dynamic simulation reveals that the coplanar arrangement of the prodrug may be primarily responsible for the formation of a long lamella-like or spherical morphology. Similarly, the natural pentacyclic triterpene of ursolic acid (UASS) was modified with disulfide and the prodrug could co-assemble with Ce6 with GSH responsiveness and good antitumor efficacy.[58]

A prodrug by conjugating two anticancer drugs cabazitaxel (CTX) via a thioketal linker was synthesized (Figure 3B-D).[59] Ce6, as a stabilizer, can co-assemble with the prodrug via multiple intermolecular interactions including hydrogen bonding, π-π stacking, and hydrophobic interactions. Upon laser irradiation, ROS produced from Ce6 not only plays effective PDT but also initiates cleavage of thioketal linker and triggers subsequent release of CTX. One major concern for conventional chemotherapy is side effects associated with systemic drug exposure. The prodrug nanoassembly realized spatiotemporal control of drug release specifically at tumor sites controlled by light with reduced systemic toxicity. Another merit of such dimeric prodrug design is that the bridged prodrugs usually have extended conjugated structure and enhanced hydrophobicity, which attributes their co-assembly with Ce6 via hydrophobic interaction and π-π stacking.[60,61] Likewise, a ROS-responsive palbociclib dimer prodrug was synthesized through conjugating palbociclib with a ROS-cleavable thioketal linker.[62] The dimer can self-assemble with Ce6 for combined chemo-photodynamic therapy with improved water solubility, stability and effective tumor accumulation. There is another research synthesizing ROS-responsive prodrug by linking PTX with polyethylene glycol (PEG) chains via thioketal linkers and then co-assembling with Ce6 to realize combined antitumor efficacy.[63]

Moreover, hydrophobic drugs can be modified with some hydrophilic molecules like oligosaccharides to increase their stability and biocompatibility. In a recent study, a glycosylated dimeric CPT prodrug was synthesized and co-assembled with Ce6 for targeted and fluorescence imaging-guided chemo-photodynamic therapy.[64] The prodrug is composed of dimeric CPT and lactose conjugated by the aromatized thioacetal, which can be cleaved in response to ROS. Light irradiation can trigger not only the generation of ROS but also the release of CPT for synergistic efficacy. Moreover, galactose residue can act as the targeting ligand to asialoglycoprotein receptor that overexpresses on HepG2 cells via carbohydrate-protein interactions. Similarly, a di-selenide bond-bridged hydroxyethyl starch-doxorubicin conjugate, HES-SeSe-DOX, was synthesized and further

combined with Ce6 to self-assemble into nanoparticles for potentiating chemo-photodynamic antitumor therapy via a cascade reaction in response to the stimuli arising from GSH, hydrogen peroxide and Ce6-induced ROS.[65] In another research, BA was modified with a water-soluble chitosan oligosaccharide and then co-assembled with Ce6 to augment the antitumor efficacy of the immune adjuvant anti-PD-L1-mediated cancer immunotherapy.[66]

The big planar structure of Ce6 provides hydrophobic and π-π stacking interactions to drive the self-assembly of Ce6 with other hydrophobic molecules. However, it is likely that Ce6 can facilitate the co-assembly of small hydrophilic molecules since it also has three ionizable carboxylic acids to interact with drugs by hydrogen bonds or electrostatic interactions. For example, Qu and co-workers reported that Ce6 can co-assemble with hydrophilic anticancer agent tirapazamine, which is dominated by hydrogen bonds and the ionization degree of drug molecules.[35] The self-assembled nanoparticles extensively improve the in vivo bioavailability of hydrophilic drugs and effectively inhibit the progression and metastasis of breast cancer via promising synergistic effects.

Taken together, the combination of Ce6 and chemo drugs highlights the opportunity to develop effective nanodrugs to treat cancer. Moreover, Ce6 can co-assemble with hydrophobic and hydrophilic small molecules by diverse interaction mechanisms. The treatment efficacy can be greatly improved by virtue of prolonged blood circulation, enhanced tumor accumulation and cellular internalization of self-assembled nanoparticles.

Apart from synthetic molecules, short peptides composed of several amino acids with pharmacological functions like cytotoxicity are attractive alternatives to self-assemble with Ce6 considering their pharmacological advantages, such as good biocompatibility, minimal immunogenicity, high tissue permeability, and rapid clearance from the blood.[67] For example, a tripeptide tyroserleutide (YSL) co-assembled with Ce6 to treat hepatocellular carcinoma was reported.[68] It was proved that YSL performed specific cytotoxicity to hepatocellular carcinoma and low toxicity to normal cells. The nanodrugs not only showed synergistic effects against hepatocellular carcinoma under laser irradiation but also exhibited enhanced drug release under acidic conditions.

To be concluded, short peptides with special biological advantages are good alternatives to form nanoassemblies with Ce6. A variety of functions can be endowed to the simple peptides owing to the flexibility for chemical modification, showcasing a perspective to construct multifunctional nanosystems with enhanced PDT effect and improved antitumor efficacy.

4.1.2 | Photothermal therapy

The major challenge for PDT-based phototherapy is hypoxia-induced low ROS generation. Another photo-based therapy, called photothermal therapy (PTT), can be an alternative to cancer treatment. Photothermal agents that can convert near-infrared (NIR) light to heat are applied in PTT to induce cancer cell apoptosis or necrosis with hyperthermia.[69] However, the suboptimal photothermal conversion efficacy is a concern. Therefore, the combination of PDT and PTT is a promising approach. The output of PTT does not rely on the oxygen level while the generation of heat can increase blood flow inside tumors, which can lead to an increase of oxygen levels in return. Furthermore, the combination of PDT and PTT can improve the efficacy of PTT in eliminating tumors with thermo-resistance under a lower temperature.[70,71]

For example, a co-assembly of fluorescence resonance energy transfer (FRET) pairs was reported (Figure 4).[72] In the study, Ce6 (FRET donor) and 1,1′- dioctadecyl-3,3,3′,3′-tetramethylindotricarbocyanine iodide (DiR, FRET acceptor) can co-assemble into nanoassemblies. The PDT effect of Ce6 is well-controlled because it is quenched by DiR and locked in the nanoassembly. The nanoassembly displayed synergetic PTT and PDT in mouse models under cascaded laser irradiation (808 and 660 nm). Moreover, it can be camouflaged by the erythrocyte membrane to prolong circulation time in the blood, increase tumor accumulation and deepen tumor penetration in vivo.

Another study reported a self-assembly of Ce6 with FDA-approved photothermal agent indocyanine green (ICG).[73] Amphiphilic ICG could self-assemble with Ce6 by π–π stacking and hydrophobic interactions, which realized the combinational effects of PDT and PTT. Moreover, the manganese ion that coordinated with the system not only enhanced the PDT effect by consuming intracellular GSH but also provided deeper imaging in biological tissues and lower signal-background ratio. The nanoparticle exhibited synergistic phototherapy with superior imaging potential for cancer theragnostic.

Under different light irradiation, the phototherapy like PDT and PTT can be achieved in a spatiotemporal and non-invasive way. With combinational therapy, heterogenic cancer cells with inherent ROS or heat resistance can be eliminated. Furthermore, heat-induced reshape of tumor microenvironment such as blood vessel expansion and tumor tissue looseness can reversibly enhance PDT efficacy.[74] In the future, more combination of PDT and PTT is anticipated with optimized light irradiation parameters and maximized treatment efficacy.

4.1.3 | DNA mispairing

The vast accumulation of ROS generated by photosensitizers is considered as a cause of oxidative DNA damage and cell apoptosis. However, the damage can be reduced or reversed by the repair pathways of aberrant DNA in tumor cells. To address the problem, two directions emerge, namely, to inhibit the repair pathways and promote the mispairing of DNA.

Etoposide (VP-16) is a typical topoisomerase II (TOP II) inhibitor and can effectively act on Ku70 protein to inhibit replication and repair process of DNA.[75] It is found that VP-16 can self-assemble with Ce6 into nanoparticles with boosted PDT-mediated cytotoxicity by inhibiting DNA repair.[76] In recent research, Kong and co-workers fabricated a self-delivery nanomedicine to elevate oxidative damage by blocking the DNA repair pathway through poly(ADP-ribose) polymerase (PARP) inhibition.[77] Ce6 and PARP inhibitor olaparib can co-assemble into nanoparticles with a high drug content and favorable water stability. Olaparib could curb the activation of PARP, upregulate the expression of γ-H2AX

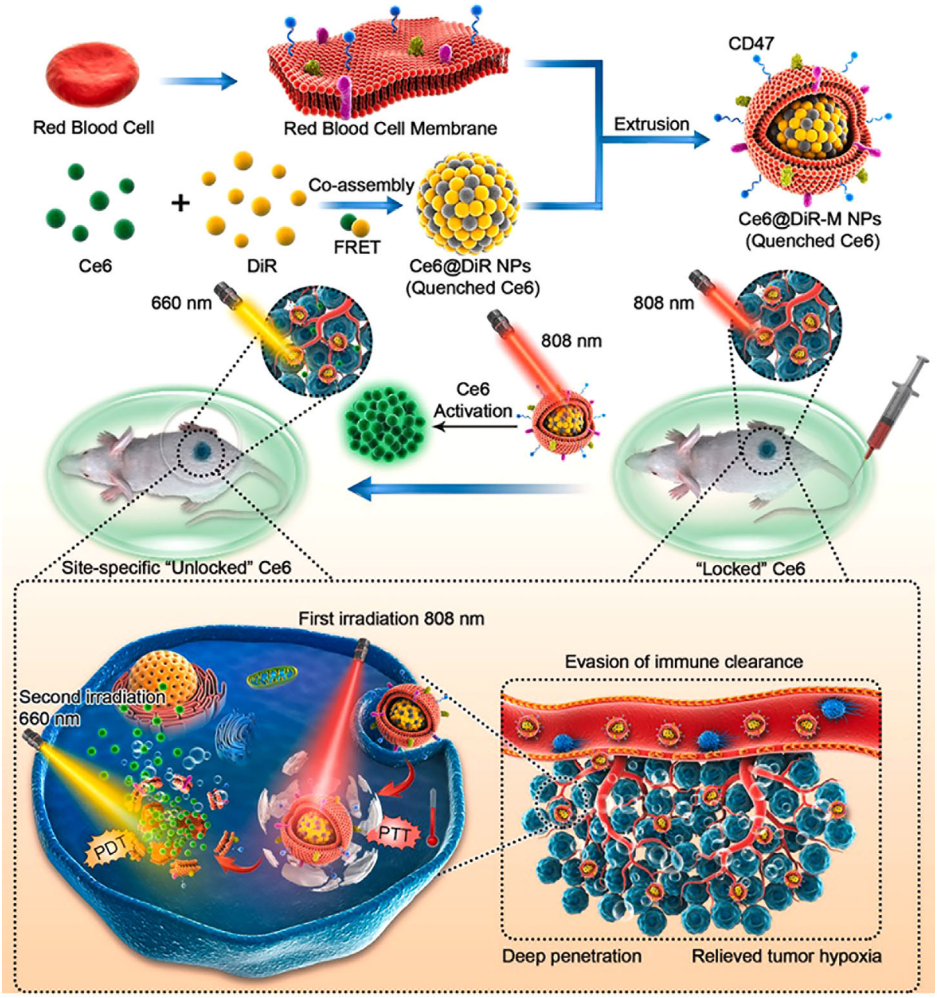


FIGURE 4 Schematic representation of the preparation of erythrocyte camouflaged Ce6@DiR nanoparticle and its programmed cascade-activatable photothermal therapy (PTT) and photodynamic therapy (PDT). Figure reproduced from Ref.[72] with permission. Copyright © 2021 the authors. Production and hosting by Elsevier B.V. on behalf of KeAi Communications Co., Ltd.

and induce the downregulation of Rad51, thereby blocking the DNA repair pathway to sensitize tumor cells for PDT. The reported platforms with DNA repair inhibition serve as a novel modality for the development of nanomedicine to overcome oxidative resistance in tumor treatment.

Apart from inhibiting the repair of DNA under oxidative stress, the promotion of mispairing of deoxynucleotides can be an alternative. Based on the strategy of reducing resistance to oxidative stress, a self-assembled nanoparticle composed of Ce6 and mut-T homolog 1 (MTH1) protein inhibitor TH588 was fabricated (Figure 5A-B).[78] By inhibiting MTH1 protein, TH588 could reduce 8-oxo-2′-deoxyguanosine triphosphate hydrolysis, facilitate mispairing of deoxynucleotide in DNA resulting from ROS-induced oxidative damage and increase DNA damage and cell apoptosis. The self-assembled nanoparticles sensitized the tumor cells to ROS and achieved excellent antitumor efficacy in vivo despite limited oxygen level by virtue of inhibiting MTH1 protein to hamper the ROS defending system.

4.1.4 | Metastasis and migration inhibition

Distant metastasis is the main cause of poor prognosis and unsatisfactory treatment outcomes of various malignancies.[79] Epithelial–mesenchymal transition (EMT) is a complicated process actively involved in the invasiveness of malignant tumors, characterized by the loss of the epithelial marker E-cadherin (E-cad) and acquisition of the pro-migratory mesenchymal marker N-cadherin (N-cad).[80] Recently, a nanoparticle comprised of Ce6 and EMT inhibitor epalrestat (Epa) for combined PDT treatment and antimetastasis was developed.[81] Epa can inhibit aldo-keto reductase family 1 member B1 (AKR1B1), which plays a key part in activating EMT and facilitating cancer progression. However, as an unsatisfactory antitumor agent, the treatment efficacy of Epa is greatly limited due to reduction of ROS. Therefore, the introduction of PDT not only combined the pharmacological function of Epa for antimetastasis but also improved the cytotoxicity of Epa by increasing ROS. The antitumor efficacy of the nanoplatform was confirmed both in vitro and in vivo.

Another example combining antiinflammatory drug molecule sulfasalazine (SAS) with Ce6 was brought up by Huang and co-workers to realize enhanced tumor-killing activity and inhibited metastasis (Figure 5C,D).[82] SAS can activate programmed ferroptosis in tumor cells and suppress the migration behavior of survived cancer cells after the treatment via deactivating the proinflammatory signaling pathway nuclear-factor kappa B (NF-κB).

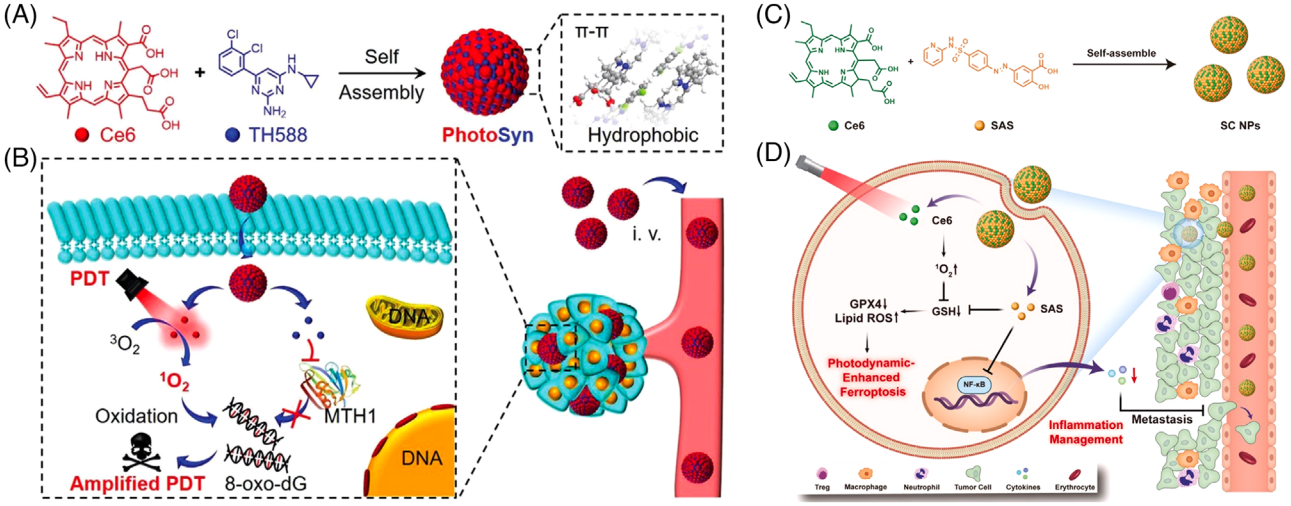


FIGURE 5 (A) Self-assembly of Ce6 and TH588 through π–π stacking and hydrophobic interaction. (B) The proposed mechanism of self-assembled nanoparticles for oxidative damage enhanced photodynamic therapy (PDT). Figure reproduced from Ref.[78] with permission. Copyright © 2021 Wiley-VCH GmbH. (C-D) Schematic diagram of the self-assembly process of Ce6 and SAS and the underlying mechanisms for oncotherapy. Figure reproduced from Ref.[82] with permission. Copyright © 2022 Elsevier B.V.

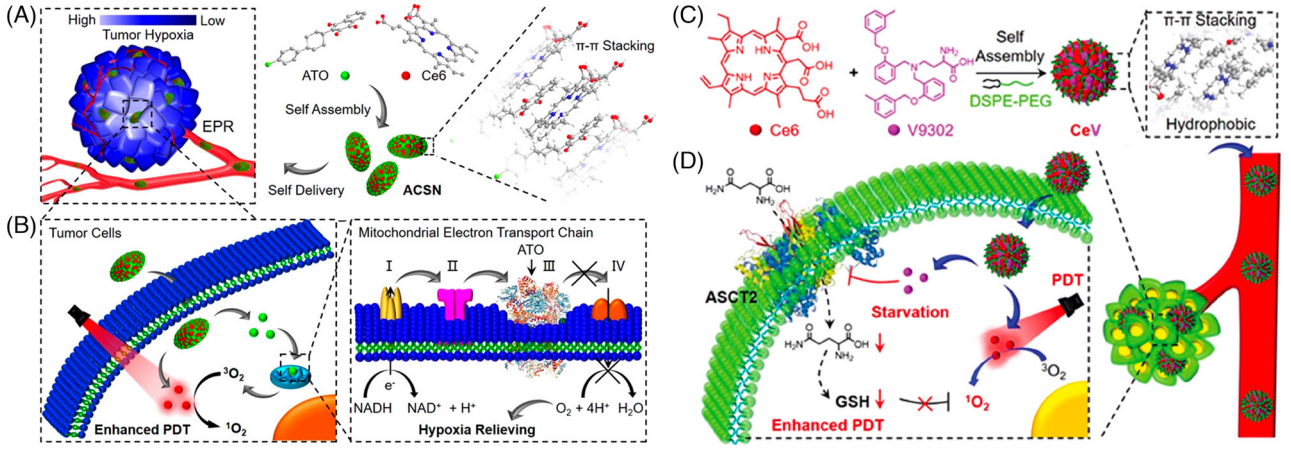


FIGURE 6 (A and B) The preparation of nanoparticles by the self-assembly of atovaquone (ATO) and Ce6 and the proposed mechanism of reduced oxygen consumption and relieved tumor hypoxia by inhibiting mitochondrial complex III in the mitochondrial electron transport chain. Figure reproduced from Ref.[30] with permission. Copyright © 2020 American Chemical Society. (C) Self-assembly of Ce6 and V9302 through intermolecular π–π stacking and hydrophobic interaction. (D) The proposed mechanism of self-assembled nanoparticles for glutamine starvation-enhanced photodynamic therapy (PDT). Figure reproduced from Ref.[91] with permission. Copyright © 2021 Wiley-VCH GmbH.

4.1.5 | Hypoxia relief

The treatment efficacy of PDT is undermined by the limited generation of ROS under tumor hypoxia environment.[83] Therefore, the combination of PDT and oxygen supplier or oxygen consumption inhibitor is a good strategy for enhancing the PDT efficacy.

For example, a self-assembled nanoparticle co-assembled with Ce6 and oxidative phosphorylation (OXPHOS) metabolic pathway inhibitor atovaquone (ATO) was constructed (Figure 6A-B).[30] ATO can efficiently inhibit OXPHOS metabolic pathway by inhibiting mitochondrial complexes in the mitochondrial electron transport chain (ETC), resulting in reduced oxygen consumption. After intravenous injection, the nanoparticles could accumulate at tumor sites by the EPR effect and inhibit ETC, enhancing Ce6-mediated PDT efficacy against hypoxia environment. The study shed light on developing analogous carrier-free nanodrugs for PDT combined with oxygen regulators against hypoxic tumor. In a recent study, a self-assembled O^2-economizer composed of Ce6 and tamoxifen was prepared to relieve hypoxia and reverse the antiapoptotic pathway for enhanced antitumor therapy.[84] Tamoxifen can effectively inhibit mitochondrial respiration to relieve hypoxia and reduce Bcl-2 expression to reverse antiapoptotic pathway, which regulates the unfavorable tumor microenvironments to enhance the PDT efficacy on tumor elimination.

The efficacy of PDT is largely dependent on oxygen consumption while it exacerbates the hypoxia environment in solid tumors by upregulating expression of hypoxia-inducible factor-1α (HIF-1α). As a potent transcriptional activator, HIF-1α functions by dimerizing with HIF-1β to form HIF-1 and subsequently initiates downstream gene transcription, such as PD-L1, GLUT-1, and VEGF to lead to immune exhaustion, cellular proliferation, and metastasis.[85] Therefore, combination of PDT and HIF-1α inhibition showcases a

potential direction for synergistic antitumor therapy. Mechanistic target of rapamycin (mTOR) was proved to be the upstream activator of HIF-1 function in cancer cells. Inhibition of mTOR by rapamycin results in blockage of HIF-1α expression and HIF-1-dependent transcription.[86]

Intriguingly, it is found that rapamycin could co-assemble with Ce6 into nanoparticles, which showed a highly promising antitumor efficacy by reversing hypoxia-mediated tumor resistance and overcoming the restriction of PDT treatment.[87] Moreover, the metal−organic frameworks (MOFs) formed by the coordination between Fe^{3+} and tannic acid (TA) were coated on the surface of the nanoparticles with effective catalase encapsulation to facilitate abundant hydrogen peroxide decomposition in solid tumors, further relieving hypoxia tumor microenvironment. A similar study has reported that 3-(5′-hydroxy-methyl-2′-furyl)−1-benzyl indazole (YC-1), as a direct HIF-1α inhibitor, can co-assemble with Ce6 through π-π stacking and hydrophobic interactions. The nanoplatform was proved to sensitize cancer cells to PDT by downregulating HIF-1α, which enhanced antitumor effects.[88]

The method via decreasing oxygen consumption represents a mature toolbox for enhanced PDT efficacy. In the future, more strategies based on reshaping tumor microenvironment to increase oxygen supply can be exploited like expanding tumor vasculature and loosening tumor tissues to facilitate oxygen transport.

4.1.6 | Other combinational therapy for sensitizing PDT

There are diverse reasons accounting for PDT resistance of tumor cells. Glutamine works as a crucial intermediate involved in many metabolic processes of cancer cells, indicating a promising antitumor strategy targeting glutamine metabolism.[89] Glutamine can be transported into cancer cells through the alanine-serine-cysteine transporter 2 (ASCT2) and then transformed into glutamate by mitochondrial glutaminase. The transformation leads to an increased generation of GSH, which would be of benefit to maintain the redox homeostasis and protect cells from oxidative stress.[90] V9302 was reported as the ASCT2 inhibitor to restrain the uptake of glutamine, resulting in a reduced GSH production and an amplified oxidative stress inside the cells. V9302 can self-assemble with Ce6 into nanoparticles, which can greatly boost the PDT efficacy by virtue of glutamine starvation (Figure 6C-D).[91] Similarly, the glutamine hydrolysis inhibitor Bis-2-(5-phenylacetamido- 1,3,4-thiadiazol-2-yl) ethyl sulfide (BPTES) can self-assemble with Ce6 and achieve remarkable antitumor efficacy in a breast cancer mouse model via sensitized PDT.[92] In the study, human serum albumin was utilized to increase the stability and biocompatibility of the system. The same strategy exploiting inhibition of the activity of glutaminase for sensitized PDT was further employed via co-assembly of Ce6 and glutaminase inhibitor compound 968 (C968).[93]

Another combination of starvation treatment with PDT was developed via co-assembly of Ce6 and glucose transporter 1 inhibitor genistein.[94] In the study, genistein not only curbed tumor growth via inhibiting glucose uptake but also amplified the therapeutic efficacy of PDT by decreasing the consumption of oxygen from tumor respiration. The starvation therapy-sensitized PDT strategy by carrier-free self-assembled nanoparticles heralds promising clinical prospects.

The heterogeneity of solid tumors also contributes to PDT resistance. Cancer stem-like cells (CSCs), which account for a small subpopulation of tumor cells, displayed inherent resistance to PDT due to expression of ROS scavengers.[95] Recently, a strategy to combine PDT with Notch pathway deactivation was reported via self-assembly of Ce6 and gamma-secretase inhibitor MK-0752 (Figure 7).[32] As one of the most important pathways regulating CSCs, the inhibition of Notch pathway can effectively inhibit cancer stemness. Cancer stemness inhibition can sensitize CSCs to PDT, resulting in significant tumor growth repression with less recurrence potential. The strategy by deactivating certain pathway to enhance the sensitivity of whole solid tumor to PDT represents a new modality for efficient combinational therapy.

Autophagy plays both sides in cellular homeostasis and metabolism, which can facilitate tumor progression but also exert an unknown impact on tumor inhibition. A nanoparticle self-assembled from Ce6 and autophagy promoter celastrol was developed with excellent PDT performance and autophagy regulation capacity.[96] The ROS generation upon PDT can amplify the oxidative stress and promote cell autophagy, which functions cooperatively with celastrol for sensitized PDT and enhanced antitumor efficacy by promoting autophagy.

The PROTAC-mediated targeted protein degradation via hijacking the ubiquitin-proteasome system has emerged as a paradigm-shifting technology and shown great therapeutic potential.[97] Cell cycle arrest stands as a promising cancer treatment strategy since the cell cycle progression in cancer cells is highly activated.[98] Recently, Wang and co-workers reported a CDK4/6 inhibition-based cell cycle arrest combinational therapy for sensitized PDT.[99] Ce6 can self-assemble with CDK4/6 PROTAC into nanoparticles for synergized anticancer effect, which was initiated by mitochondria accumulation and activation, resulting in elevated production of ROS and cell apoptosis rate. Moreover, PDT-induced immunogenic cell death cooperatively remodelled immunosuppressive tumor microenvironment for enhanced antitumor immunity. The combination of G1 cell cycle blockade and PDT advanced the broad application of PROTAC in clinical cancer treatment.

4.2 | Modulating tumor microenvironment

Apart from directly interacting with tumor cells, modulating tumor microenvironment like activating immune system and inhibiting neovascularization represents a promising strategy to effectively treat cancers combined with PDT.

4.2.1 | Immunotherapy

Recently, stimulating the host immune system represents a promising tactic to treat cancer, especially in controlling metastatic tumor growth.[100] However, tumor cells often evade immune attack by upregulating immunosuppressive molecules and recruiting various

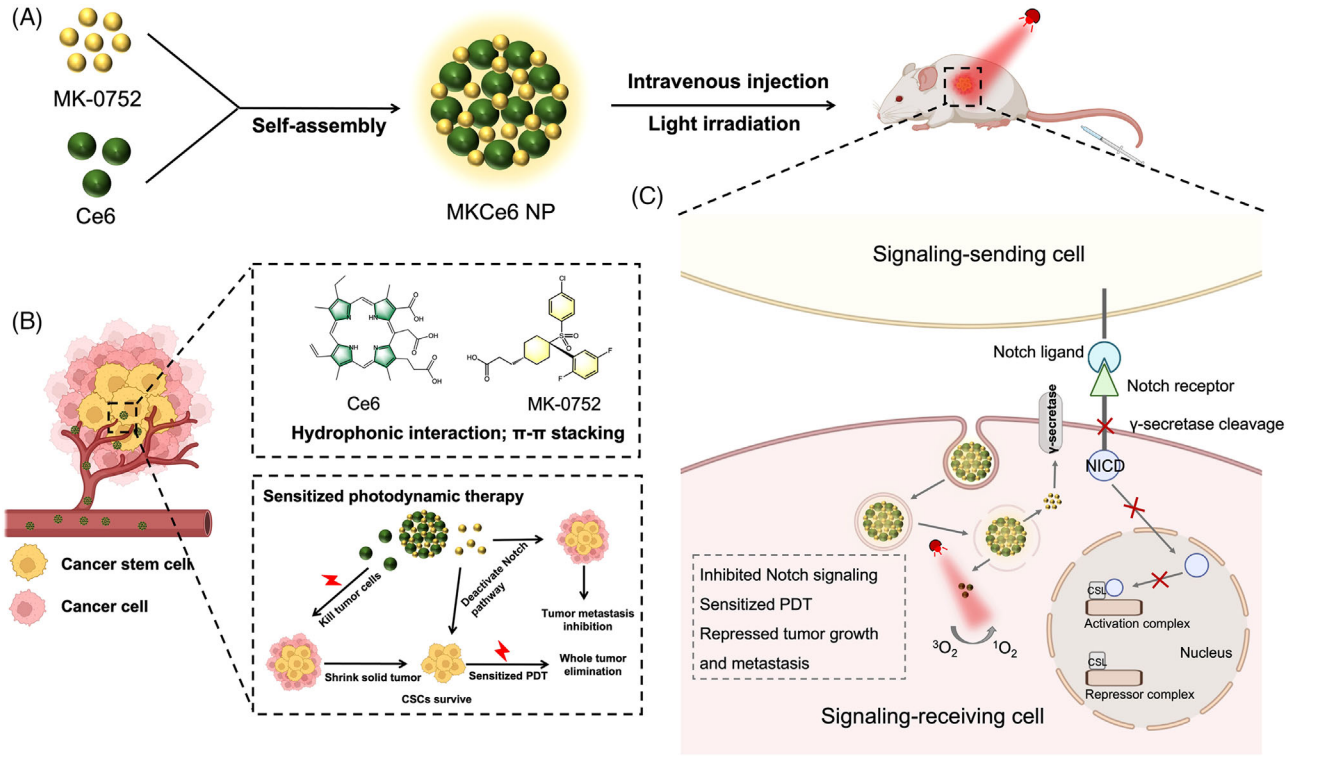


FIGURE 7 Schematic illustration of cancer stemness inhibition-enhanced photodynamic therapy (PDT). (A) Self-assembly of Ce6 and MK-0752 into MKCe6 nanoparticles (NPs). (B) Therapeutic effects of MKCe6 NPs in tumor growth inhibition. PDT effect of Ce6 can kill tumor cells and shrink solid tumor, while MK-0752 inhibits Notch pathway to inhibit cancer stemness, sensitize cancer stem-like cells (CSCs) to PDT, and inhibit tumor cells metastasis. (C) The molecular mechanisms of PDT effect and inhibition of Notch pathway by MKCe6 NPs in tumor cells. Figure reproduced from Ref.[32] with permission.

immunosuppressive cells.[101] Recent research indicated that PDT could trigger an ICD cascade to elevate tumor sensitivity towards immunotherapy.[102] Therefore, the combination of PDT and immune modulators has become a feasible strategy to boost antitumor immunity by reversing tumor immunosuppressive environment.

The first study on the combination of Ce6 with immune modulators reported the self-assembly of Ce6 and immune checkpoint inhibitor BMS-202, which can elicit tumor immunity and antimetastatic effect on breast cancer.[103] Programmed cell death 1 (PD-1) / programmed cell death ligand 1 (PD-L1) is a well-documented immune checkpoint. BMS-202 can effectively inhibit PD-1 and PD-L1 interaction via inducing PD-L1 dimerization.[104] The self-assembled BMS-202 nanoparticles efficiently inhibited not only primary tumors but also distant tumors with comparable treatment effect of anti-PD-L1 antibody, accompanying enhanced dendritic cell maturation and infiltration of antigen-specific T cells into tumor sites. Moreover, BMS-202 nanoparticles could kill and attack spreading metastatic lung cancer cells and offer immune-memory protection to prevent tumor recurrence.

Next, a self-delivery photo-immune stimulator by noncovalent interaction between Ce6 and NLG-919 to initiate potent antitumor immune responses was developed (Figure 8A-B).[33] NLG-919 could effectively inhibit an overexpressed enzyme in tumor cells, called indoleamine 2,3-dioxygenase 1 (IDO-1). The inhibition of IDO-1 can reverse tumor immunosuppressive microenvironment via curbing amino acid L-tryptophan (Trp) depletion and Kynurenine (Kyn) accumulation, which results in reduced intratumor infiltration of regulatory T cells (Tregs) and enhanced T-cell responses.[105] At the same time, Ce6 could exert robust PDT effects on primary tumors. The produced neoantigen can promote DCs maturation and migration, recruit and activate cytotoxic T lymphocytes (CTLs) for synergized immunotherapy. To sum up, the self-assembled photo-immune stimulators could realize an effective inhibition on both primary and distant tumor growth by photodynamic-sensitized immunotherapy.

More recently, a nanosystem co-assembled from Ce6 and tazemetostat (Taz) through intermolecular interactions was developed.[106] Taz could inhibit the epigenetic regulator of EZH2 to suppress the methylation of H3K27, which would promote tumor cells to express MHC-I and release CXCL10. Consequently, the epigenetically reprogrammed tumor cells are readily recognized by effector T cells to enhance antitumor immunity. Furthermore, Ce6-induced PDT can generate ICD, resulting in a simultaneous inhibition of the growth of primary and distant tumors with low systemic toxicity.

Furthermore, Ce6 can facilitate two molecules' self-assembly to achieve combinational therapy with immunotherapy. For example, BMS-1 (PD-1/PD-L1 inhibitor), V9302 (ASCT2 inhibitor) can co-assemble with Ce6 into nanoparticles and achieve boosted immune recognition and prevention from immune escape for metastatic tumor eradication by reprogramming glutamine metabolism.[107] In another research, Ce6 facilitated the co-assembly of BMS-1 and NLG-919 into nanoparticles, which not only achieved inhibited tumor proliferation but also induced ICD response to activate immunological cascade.

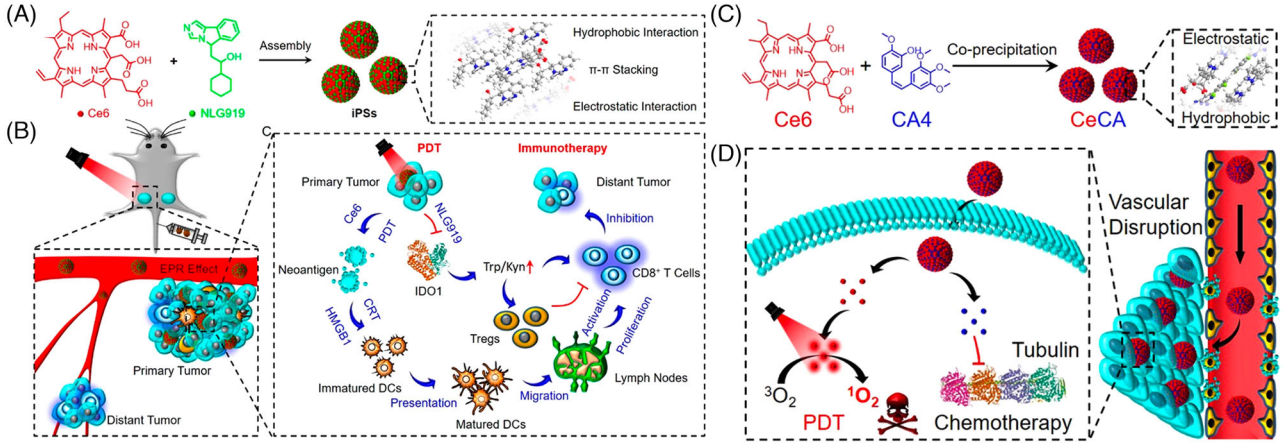


FIGURE 8 The combination of photodynamic therapy (PDT) with functional molecules that regulate tumor microenvironment (TME). (A and B) The preparation and the proposed mechanism of self-assembled nanoparticles via Ce6 and NLG919 for growth inhibition of primary and distant tumors by PDT-sensitized immunotherapy. Figure reproduced from Ref.[33] with permission. Copyright © 2020 American Chemical Society. (C and D) The synthesis and the proposed mechanism of self-assembled nanoparticles via Ce6 and CA4 for vascular disruption supplemented chemotherapy and PDT. Figure reproduced from Ref.[112] with permission. Copyright © 2021 Elsevier Inc.

Ultimately, the nanoparticles tremendously suppressed tumor growth and metastasis, while leading to a minimized side effect.[108]

Together, these studies indicate that the co-delivery of Ce6 and immune modulators displayed strong antitumor effect with reduced metastasis and recurrence. Inhibitors of other immune checkpoints like cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) can also be considered as candidates for synergized immunotherapy with PDT.

4.2.2 | Antiangiogenesis therapy

Another widely used strategy for antitumor therapy is antiangiogenic therapy, which aims to suppress the development of vasculature that supports the growth and metastasis of tumor cells using tumor angiogenesis inhibitors. The inhibitor can induce the apoptosis of vascular endothelial cells, destroy the angiogenesis net, and cut off the supply of nutrients and oxygen to the tumors.[109] Worse yet, incomplete PDT might elicit cytokines and growth factors to promote tumor angiogenesis.[110] Consequently, the combination of vasculature-targeted therapy and PDT would not only improve the antitumor efficiency, but also surmount its therapeutic limitations.

A self-assembled nanoparticle comprised of Ce6 and antiangiogenesis inhibitor sorafenib was constructed to achieve distinct antitumor efficacy due to enhanced PDT effect and disruption of tumor blood vessels.[111] The nanoparticle exhibited good biocompatibility and biosafety while killed cancer cells with a rather low dose (200 μg/kg) in vivo, showing great promise towards clinical translation. An additional example that combines antiangiogenesis therapy with PDT has also shown synergistic effect (Figure 8C-D).[112] The authors construct a nanosystem self-assembled by Ce6 and combretastatin A4 (CA4). CA4 acted as the chemotherapeutic agent for tumor inhibition and vascular disruption.[113] More importantly, Ce6-induced PDT could synergistically disrupt the vasculature with CA4-mediated endothelial cell inhibition to cause tumor hemorrhage for enhanced chemo-photodynamic therapy. Ultimately, this vascular disruption-supplemented synergistic treatment greatly inhibited tumor proliferation and even achieved almost tumor eradication.

5 | CONCLUSION AND FUTURE PERSPECTIVE

In this review, we summarized recent advances in the design and development of Ce6-based self-assembled nanoparticles. The self-assembled nanoparticles exhibit advantages over free drug molecules owing to improved water solubility, prolonged blood circulation, and enhanced tumor penetration. The carrier-free characteristics endow the Ce6-based nanoparticles with ultrahigh drug loading capacity and good biocompatibility. Moreover, the driving forces behind the self-assembly were discussed, providing a likely prediction for the chemical structure of other molecules that can co-assemble with Ce6. The molecules usually have conjugated structure, protonable groups and/or hydrophobicity that can strongly interact with Ce6. The pharmacological function of the molecules varies from directly interacting with tumor cells to modulating tumor microenvironment. The molecules can be synthetic small molecules and peptides, which greatly widens the variety of building blocks for constructing Ce6-based nanoparticles. Besides, small functional molecules are structurally simple, and generally easy to design and modify compared with structurally complex polymers.

The advantages of Ce6-based nanomaterials include good stability, easy modification, high biocompatibility, controlled release of drugs and photosensitizers, enhanced cell internalization, and improved pharmacological functions. Based on the studies summarized in this review, the nanomaterials assembled from Ce6 present the potential for various combination therapy like immunotherapy, chemotherapy, phototherapy, antiangiogenesis therapy, etc. The small molecules are easily modified with diverse functional groups and responsive linkers, which endowed the assemblies with targeting ability and responsiveness to diverse stimuli, respectively.

Nevertheless, several challenges remain to be addressed for the successful clinical translation of these systems. Firstly, although Ce6-based nanoparticles can be obtained through simple and one-step nanoprecipitation, precise control of self-assembly to produce uniform and stable nanoparticles and minimize batch-to-batch variation is crucial for scaled-up manufacturing. Secondly, the colloidal stability of Ce6-assembled nanoparticles is mainly tested in vitro, whereas there is lack of comprehensive investigations into their in vivo stability and half-life under physiological conditions. Furthermore, additional biological functions of Ce6-based nanoparticles are anticipated. The last but not the least, clinical application of PDT is predominantly limited to small superficial lesions. As a result, precise light illumination is required, which could be addressed with the development of advanced optical technologies such as optical fibers and implanted LEDs.

Future research can focus on three aspects to further develop Ce6-based nanoparticles for biomedical applications and promote their eventual translation to clinical settings: (1) investigating the molecular assembly mechanisms and conditions that regulate the assembly processes; (2) identifying more suitable building blocks and functional molecules with responsiveness and targeting capabilities; (3) developing advanced light delivery techniques to expand the application of the nanosystems. A deep understanding of assembly mechanisms can facilitate the development of more reliable and controllable molecular assemblies with outstanding properties, enabling large-scale industrial production. By exploring additional building blocks, novel combination therapies with improved therapeutic efficacy and new biologically stable nanomaterials can be constructed for the treatment of a wide range of relevant diseases. The advancement of new light-delivery technologies will likely broaden the applications of Ce6-based nanoparticles and facilitate their translation from bench to bedside. Overall, the flexibility, diversity and adjustability of self-assembly systems herald a promising future for Ce6-based nanotechnology.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest to declare.

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